Somatostatin receptor-mediated imaging and therapy: basic science, current knowledge, limitations and future perspectives

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Abstract. In vivo somatostatin receptor-mediated scintigraphy has proven to be a valuable method for the visualisation of neuroendocrine tumours and their metastases. A new application is the use of radiolabelled analogues for somatostatin receptor-mediated therapy. This paper presents a review on the basic science, historical background and current knowledge of somatostatin receptor subtypes and their expression in neuroendocrine tumours. New somatostatin analogues, new chelators, "new" radionuclides and combinations thereof are also discussed. Due attention is given to limitations and future perspectives of somatostatin receptor-mediated imaging and therapy.

Keywords: Somatostatin receptor subtypes – Imaging – Therapy – DTPA – DOTA

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Historical background

Peptide receptor imaging with radiolabelled peptides is a sensitive and specific technique to demonstrate the presence of receptors on various tumours in vivo (see [1, 2, 3] and references therein). With this technique, receptor-positive primary tumours and metastases can be visualised. As soon as the success of peptide receptor imaging for tumour visualisation became clear, the next logical step was to label these peptides with radionuclides emitting α- or β-particles, including Auger or conversion electrons, and to perform peptide receptor radionuclide therapy (PRRT).

Since somatostatin-14 (somatostatin) and its analogues are the most frequently used of all peptides for imaging and PRRT, their application is the main focus here. This review covers elements of the basic science and preclinical and clinical aspects of somatostatin receptor-mediated imaging (SRI) and therapy. New analogues, chelators, radionuclides and combinations thereof are discussed. Limitations and potential future directions are also considered.

Somatostatin is a cyclic disulphide-containing peptide hormone of 14 amino acids. It is present throughout the central nervous system (CNS), including the hypothalamus, the cerebral cortex and the brain stem, and in the gastrointestinal tract, such as the pancreas. Somatostatin receptors have been identified in the CNS, the gastrointestinal tract, and on many cells of neuroendocrine origin. However, non-neuroendocrine cells, such as lymphocytes, also possess these receptors. In the CNS, somatostatin acts as a neurotransmitter, while its hormonal activities include the inhibition of the release of growth hormone, insulin, glucagon and gastrin. The general inhibitory effect of somatostatin on hormone secretion of various glands led to the concept of possible beneficial effects of somatostatin in the treatment of diseases based on gland hyperfunction or overproduction of hormones by endocrine-active tumours. However, somatostatin itself turned out to be unsuitable for such treatment. After intravenous administration in man, somatostatin has a plasma half-life of ≈3 min, owing to rapid enzymatic degradation. As long ago as the early 1980s, somatostatin analogues were developed that were more resistant to enzymatic degradation than somatostatin itself. The molecule was modified in various ways while preserving most of the biological activity of the original molecule. Introduction of D-amino acids and shortening of the mol-

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ecule to the bioactive core sequence resulted in eight amino acid-containing somatostatin analogues such as octreotide (sandostatin, formerly also known as SMS 201-995), lanreotide (BIM23014) and RC-160 (vapreotide) (for structural formulae, see Fig. 1). Lanreotide and octreotide are widely used for the symptomatic treatment of neuroendocrine-active tumours, such as growth hormone-producing pituitary adenomas and gastroenteropancreatic tumours. The biology and clinical application of somatostatin and somatostatin analogues have been described extensively (see [4, 5] for reviews and references therein).

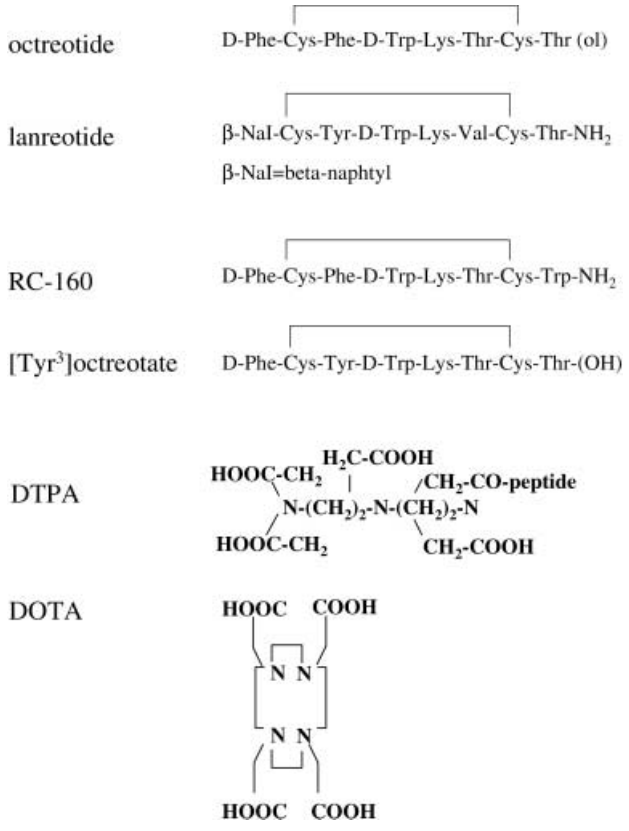

Fig. 1. Structural formulae of various eight amino acid-containing somatostatin analogues and chelators

Somatostatin receptor subtypes

Somatostatin receptors have been described in a large number of human primary tumours and cell lines. With the use of different radioiodinated somatostatin analogues it was possible to differentiate somatostatin receptors pharmacologically. Initially, two somatostatin receptor classes were described: class 1 was defined as displaying a relatively high affinityfor the biologically stable ligands, such as octreotide, while class 2 had no affinity for the latter. More recently, five different human somatostatin receptor types (sst) have been cloned and splice variants reported. These have been named sst1–5, according to chronological order of discovery. Each sst is the product of a single gene located on a different chromosome. This allows a tissue-specific regulation of their expression and suggests diverse functions of the somatostatin receptors in different organs. Structurally, the sst's belong to the family of G protein-coupled receptors characterised by seven transmembrane domains. The extracellular part is responsible for the ligand binding, while the intracellular domains transduce the signal into the cell[5, 6]. Four of the genes are intronless, the exception being *sstr2* [7]. The sst2 comprises two isoforms generated from the same gene: sst2a, the unspliced form, and sst2b, a 23 amino-acid shorter splice variant [8]. The function of the sst2b is currently unknown. All subtypes bind somatostatin and somatostatin-28 (a polypeptide of 28 amino acids with somatostatin at its C-terminus) with high affinity, while the affinities of numerous somatostatin analogues for the five sst's differ considerably. Pharmacological studies in cells transfected with complementary DNA encoding the various somatostatin receptor

Table 1. Affinity profiles (IC_{50}) for human sst1–sst5 receptors of a series of somatostatin analogues (adapted from Reubi et al. [9])

Peptides	sst1	sst2	sst3	sst4	sst5
Somatostatin-28	5.2±0.3	2.7±0.3	7.7±0.9	5.6±0.4	4.0±0.3
Octreotide	>10,000	2.0±0.7	187±55	>1,000	22±6
[DTPA^0]octreotide	>10,000	12±2	376±84	>1,000	299±50
[In-DTPA^0]octreotide	>10,000	22±4	182±13	>1,000	237±52
[DOTA^0]octreotide	>10,000	14±3	27±9	>1,000	57±22
[DTPA^0,Tyr^3]octreotate	>10,000	3.9±1	>10,000	>1,000	>1,000
[DOTA^0,Tyr^3]octreotide	>10,000	14±3	880±324	>1,000	393±84
[Y-DOTA^0,Tyr^3]octreotide	>10,000	11±2	389±135	>10,000	114±29
[DOTA^0,Tyr^3]octreotate	>10,000	1.5±0.4	>1,000	453±176	547±160
[Y-DOTA^0,Tyr^3]octreotate	>10,000	1.6±0.4	>1,000	523±239	187±50

Studies were performed on cells stably transfected with the five different human somatostatin receptor subtypes, using ^{125}I-[Leu^8, D-Trp^{22}, Tyr^{25}]-somatostatin-28 as the universal radioligand and the peptides, both labelled (In, indium; Y, yttrium) and unlabelled, as competitors at increasing concentrations. All values are IC_{50}±SEM in n*M*

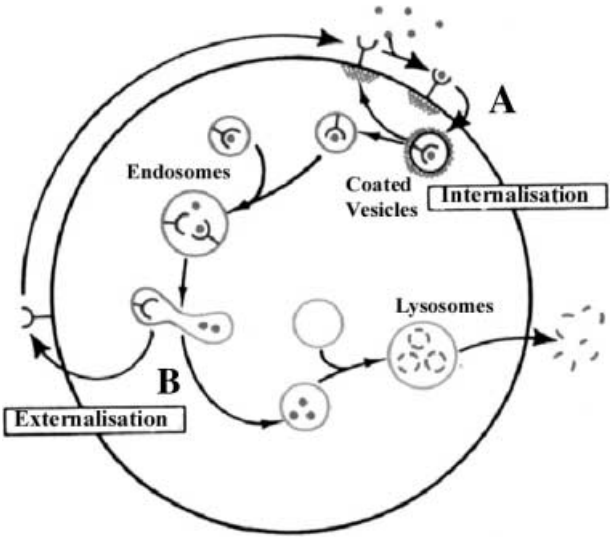

Fig. 2. A basic model for receptor-mediated endocytosis. After binding of the (radio)ligand to its receptor (**A**), the receptor-ligand complex is internalised via invagination of the plasma membrane and coated vesicles. The resultant intracellular vesicles, termed endosomes, rapidly acidify, which causes the ligand to dissociate from the receptor (**B**). The ligand is transported to the lysosome for processing, and the receptor recycles back to the plasma membrane (externalisation). The whole process takes approximately 15 min. The polarity of the DTPA-conjugated radiometabolites, such as ^{111}In-DTPA-D-Phe prevents passage across the lysosomal and cell membranes [19]. (Adapted from P. Weigel [60])

subtypes have demonstrated that the sst2a, sst3 and sst5 receptors correspond to the formerly named class 1 receptors. The sst1 and sst4 receptors correspond to class 2. Recently the affinity profiles (IC_{50}) for human sst1–5 of a series of somatostatin analogues have been reported (Table 1) [9]. Therefore, SRI with radioactive somatostatin analogues is based on the visualisation of octreotide-binding somatostatin receptors: sst2, 3 and 5 (for reviews: [2, 4], and references therein).

In a recently published and impressive review by Patel [10], it is postulated that in most instances somatostatin receptor subtypes operate in concert, rather than as individual members. Nonetheless, there is evidence for sst-selective actions, such as arrest of cell growth through sst1, 2, 4 and 5, and unique cytotoxic actions by sst3. It was also reported by Patel's group that somatostatin receptor subtypes have different rates of internalisation: sst3 has the highest rate and sst1 even fails to internalise (for internalisation in general, see 2 and the section "PRRT"). For small and rapidly degradable (radio)ligands that do not (or hardly) internalise, the result will be a short residence time of the radioactivity at their target, which might hamper their application in nuclear medicine. However, most of these models are in vitro models and still have to be proven in vivo ([10], and references therein). Discussion of these subjects in more detail is beyond the scope of this article.

Evaluation of the somatostatin receptor expression in tumours

As mentioned above, all human somatostatin receptor subtypes bind somatostatin and somatostatin-28 with high affinity (see Table 1). The distribution of the somatostatin subtypes in somatostatin receptor-positive tumours is listed in Table 2. The reported results were obtained by reverse transcriptase polymerase chain reaction (RT-PCR) or by in situ hybridisation to evaluate the somatostatin receptor subtype expression at the mRNA level. An advantage of the in situ hybridisation technique compared with the RT-PCR technique is the simultaneous provision of morphological information, but a disadvantage is its lower sensitivity. With RT-PCR, however, very small tissue samples can be used for the quantitation of RNA. With a sample representing as few as one million cells (≈1 mg of tissue), a sensitive RT-PCR is able to detect 100 copies of mRNA. The detection thereof doesnot necessarily represent the sample as a whole, since it could be a result of one cell with 100 copies or 10 cells with 10 copies of mRNA. Samples such as tumour biopsies with a heterogeneous somatostatin receptor subtype distribution can give false-negative results, while tissue samples that include nerves which are part of the CNS can give false-positive results. Another, though less sensitive technique is immunohistochemistry using specific antibodies directed against the different somatostatin receptor subtypes. Nowadays, specific antibodies directed against sst1, sst2a and sst3 are available. However, very few data obtained with this technique have been reported.

Wulbrand et al. reported an overview of somatostatin receptor subtype expression on the four most frequent neuroendocrine tumours (Table 2, [11]). In general, sst1, sst2 and to a lesser extent sst5 are expressed. All studies showed a low incidence of sst3 expression in gastrinomas and carcinoids.For sst4, incidences varying from 22% to 86% have been reported. However, the authors have several explanations for these variations, such as the origin of the samples (i.e. pancreatic vs extrapancreatic, primary vs metastases). These findings emphasise that radiolabelled analogues that bind all somatostatin receptor subtypes, as well as analogues that are somatostatin receptor subtype-selective, are very welcome for further research (see also "Future directions").

Effect of dose and specific activity on biodistribution

In in vitro experiments involving saturable protein binding processes (i.e. radio-immunoassays and receptor binding studies), the signal to background ratio is often improved by lowering the mass of the radioligand and/or by increasing its specific radioactivity. Due to competition with the labelled peptide for the same receptor, the presence of un-

Table 2. Comparison of the expression frequencies of somatostatin receptor subtypes as reported in the literature (adapted from Wulbrand et al. [11])

Reference	Method	Probes (*n*)	Expression frequency of SSTR (%)				
			1	2	3	4	5
Gastrinoma							
Schaer et al. [29]	In situ	5	80	100	20	ND	50
Jais et al. [54]	RT-PCR	14	64	86	50	86	86
Jonas et al. [55]	RT-PCR	3	66	100	0	ND	ND
John et al. [56]	RT-PCR	3	66	100	33	66	100
Wulbrand et al. [11]	RT-PCR	9	100	100	22	22	100
Insulinoma							
Kubota et al. [57]	RT-PCR	4	100	75	50	100	0
Schaer et al. [29]	In situ	2	100	0	50	ND	50
Jais et al. [54]	RT-PCR	5	60	100	80	100	100
Jonas et al. [55]	RT-PCR	1	100	100	0	ND	ND
John et al. [56]	RT-PCR	3	100	100	100	100	0
Wulbrand et al. [11]	RT-PCR	10	70	90	10	20	60
Carcinoid syndrome							
Reubi et al. [58]	In situ	10	40	70	20	ND	ND
Vikic-Topic et al. [59]	RT-PCR	15	87	93	53	40	ND
Schaer et al. [29]	In situ	11	64	64	9	ND	46
Jais et al. [54]	RT-PCR	6	83	100	17	100	100
Jonas et al. [55]	RT-PCR	6	50	100	0	ND	ND
John et al. [56]	RT-PCR	9	88	100	33	44	44
Wulbrand et al. [11]	RT-PCR	9	44	67	0	33	56
Functionally inactive tumours							
Jais et al. [54]	RT-PCR	10	70	100	50	70	80
Wulbrand et al. [11]	RT-PCR	9	22	67	0	11	22

In situ, In situ hybridisation; RT-PCR, reverse transcriptase polymerase chain reaction

labelled [DTPA^0]octreotide in [^{111}In-DTPA^0]-octreotide (radioindium-labelled octreotide, OctreoScan) may have a negative effect on the percent dose uptake of radioactivity. In general, more than 90% of the peptide mass administered with [^{111}In-DTPA^0]octreotide is unlabelled. Therefore, the effects of administration of the unlabelled ligand were studied. The results showed that, contrary to what was expected, the percentage uptake of [^{111}In-DTPA^0]octreotide in octreotide receptor-positive tissues is not optimal at the lowest possible dose of maximum specific radioactivity. Rather, the uptake expressed as percent of the administered dose is a bell-shaped function of the injected mass. This was also found to be true for other radioligands [12, 13, 14]. This finding might be the result of a positive effect of increasing amounts of ligand on, for instance, the rate of internalisation (e.g. mediated by ligand-induced receptor clustering) and a negative effect of competition for the same receptor by non-radioactive ligand. This implies that the sensitivity of detection of somatostatin receptor-positive tumours by SRI might be improved by varying the mass of ligand [15]. These findings have also been confirmed in patients, in whom it was shown that coupling a standard dose of 220 MBq ^{111}In to less than 5 µg [DTPA^0]octreotide led to decreased quality of imaging with a significantly reduced uptake in tumours [16]. Therefore, [^{111}In-DTPA^0]octreotide scans should always be performed with at least 10 µg peptide (as supplied in the OctreoScan kit formulation).

PRRT

Studies on the internalisation of radiolabelled [DTPA^0]octreotide in vitro and in vivo revealed this process to be somatostatin receptor-mediated and temperature dependent [15, 17, 18]. After internalisation of the radiopharmaceutical in the cells, the radioligand is closer to the nucleus. The polarity of the DTPA-conjugated radiometabolite, such as ^{111}In-DTPA-D-Phe, prevents passage across the lysosomal and/or cell membranes [19]. This is in contrast to the situation with radioiodinated analogues, since they are rapidly degraded in vivo to radioiodinated tyrosine with subsequent release from the cell,

Table 3. Physical constants of ^{90}Y, ^{111}In and ^{177}Lu

	$t_{1/2}$ (days)	E_β (keV)		Range in tissue (μm)	
		Average	Max.	Average	Max.
^{90}Y	2.67	935	2,270	4×10^3	12×10^3
^{111}In	2.83				
IC			144–245		200–550
Auger			0.5–25		0.02–10
^{177}Lu	6.71	149	497	0.5×10^3	2×10^3

IC and Auger, Internal conversion and Auger electrons, respectively

hampering their application for PRRT. Figure 2 illustrates the process of receptor-mediated endocytosis in general.

^{111}In emits not only γ-radiation, which is visualised during scintigraphy, but also short-ranged Auger electrons. As the radiotoxicity of Auger electrons is very high if the DNA of the cell is within the particle range ([20], and references therein), an effect on tumour proliferation could be expected. Since the energy of conversion and Auger electrons is usually less than that of β-particles, their linear energy transfer (LET) and consequently their cell killing capacity is larger than that of β-particles. In general, the LET (expressed in keV per μm, and a parameter for cell kill probability) for Auger electrons is 1.1–17 and the maximal range in tissue is between ≈20 nm and 15 μm, while for β-particles with energies between 150 and 2000 keV, the LET is 0.2–0.8 with a range of 40–4000 μm ([21], see Table 3). Therefore, the radiotoxicity of a radionuclide with a highLET is very high when it is located within a few nanometres of the DNA in the nucleus. Non-homogeneous distribution of the receptors throughout the target results in heterogeneous deposition of the radionuclide. In the case of a radionuclide which emits high LET particles, the radiation dose will also be heterogeneous ([22, 23, 24], see also section "PRRT: Clinical Role").

New analogues and radionuclides for SRI and PRRT

[^{111}In-DTPA^0]octreotide is not the ideal radioligand for SRI and PRRT. One of its shortcomings is that it is labelled with the cyclotron product ^{111}In. Therefore, ^{99m}Tc-labelled somatostatin analogues have been developed and are currently in clinical trials [25, 26, 27, 28]. The lower affinity of [DTPA^0]octreotide for sst3 and the absence of affinity for sst1 and sst4 may be regarded as another shortcoming of [^{111}In-DTPA^0]octreotide. However, the vast majority of somatostatin receptor-expressing tumours express sst2, including gastroenteropancreatic tumours (see also "Evaluation of the somatostatin receptor expression in tumours" and Table 2). In addition, the presence of sst2 and/or sst5 is not a prerequisite for positive imaging. Thymus tumours expressing sst3 but not sst2 or sst5 accumulate [^{125}I-Tyr^3]octreotide in vitro [29, 30] or [^{111}In-DTPA^0]octreotide in vivo and can thus be visualised [31, 32]. This might indicate that the affinity of the radioligand for the receptor, as well as the efficiency of internalisation of the receptor-ligand complex, plays a dominant role in determining the uptakein receptor-positive tissues in vivo, and thus in the success of SRI. As mentioned earlier, octreotide has no affinity for sst1 or sst4; the only tumour type known from the literature to selectively express sst1 is the primary prostate tumour [33], while tumours expressing sst4 have not been reported.

Analogues in vitro and in vivo

Recently a comparison and evaluation of ^{111}In-chelator-peptide constructs was reported with respect to octreotide receptor-mediated binding and internalisation, as well as biodistribution in tumour-bearing rats [18]. The analogues tested included [DTPA^0,Tyr^3]octreotide and [DTPA^0,Tyr^3]octreotate. In these analogues, Phe^3 was replaced with Tyr to increase the hydrophilicity and enable radioiodination. In [Tyr^3]octreotate the C-terminal threoninol was replaced with the native amino acid threonine of octreotide to investigate the effects of an additional negative charge on clearance and cellular uptake. In addition, [DOTA^0,Tyr^3]octreotide and [DOTA^0,Tyr^3]-octreotate were synthesised and tested (DOTA=1,4,7,10-tetraazacyclo-dodecane-*N′*,*N″N‴*,*N⁗*-*t*etraacetic *a*cid, see Fig. 1). In in vitro studies, high and specific binding to the somatostatin receptors was observed, with IC_{50} values in the low nanomolar range [9]. This study also showed that these replacements, but also the metal complex, have significant influences on the affinity profiles (see Table 1), and may also be relevant for the development of other peptide radioligands [9]. Especially the sst3 and sst5 affinities were influenced by the above-mentioned replacements (i.e. Phe^3→Tyr, Thr(ol)→Thr, and unlabelled vs (Y or In)-labelled, see Table 1). Comparison of specific internalisation of ^{111}In-labelled compounds in two somatostatin receptor-positive cell lines showed that internalised radioactivity was by far the highest after incubation with [^{111}In-DTPA^0,Tyr^3]octreotate, an observation that has been confirmed in vivo in rats [18] and in humans [34].

DOTA analogues and "new" radionuclides

The DOTA compounds can be radiolabelled stably with ^{111}In, ^{90}Y and ^{177}Lu. ^{90}Y is a β-particle emitter, with a maximum energy of the electrons of 2.3 MeV, and a mean range of several millimetres in tissue. ^{177}Lu is a β-particle emitter, with a maximum energy of 0.5 MeV, and a mean tissue range of approximately 1 mm (for

physical constants, see Table 3). ^{177}Lu is also a γ-emitter (113 and 208 keV, abundance 6% and 11%, respectively) which enables visualisation with a gamma camera and thus tumour dosimetry and staging. Comparison of the physical constants of ^{90}Y and ^{177}Lu (Table 3) suggests that ^{90}Y-labelled analogues are more suitable for PRRT of larger tumours [35]. Preclinical studies and ongoing clinical trials regarding therapy of somatostatin receptor-positive tumours with [^{177}Lu-DOTA^0,Tyr^3]octreotate have yielded promising results ([36, 37], manuscripts in preparation).

PRRT: clinical role

[^{111}In-DTPA^0]octreotide therapy

PRRT with high doses of [^{111}In-DTPA^0]octreotide has been performed in a clinical phase I study. In 30 end-stage patients with mostly neuroendocrine tumours, who received a cumulative dose of up to 74 GBq, the only side-effects were a transient decline in platelet counts and lymphocyte subsets [38]. Of 21 patients who received a cumulative dose of more than 20 GBq, a reduction in tumour size was found in six and stable disease in eight. There was a tendency towards better results in patients with a high tumour uptake [38]. In a recent review by McCarthy et al., responses of 62%–69% were reported in 85 patients with metastatic neuroendocrine tumours treated with high doses (6–19.6 GBq) of [^{111}In-DTPA^0]octreotide specifically targeting tumour somatostatin receptors [39].

[^{90}Y-DOTA^0,Tyr^3]octreotide therapy

Since the particle range of the Auger electrons is small and thus has a short tissue penetration, ^{111}In-coupled peptides may not always be the ideal radiopharmaceutical for PRRT. Human PRRT trials with [^{90}Y-DOTA^0,Tyr^3]octreotide are ongoing ([40, 41], Krenning, Kvols, and Pauwels in the Novartis B151 trial). A recent analysis of the results of [^{90}Y-DOTA^0, Tyr^3]octreotide treatment in a phase I study in 22 end-stage patients with progressive disease showed a partial tumour response in two patients, a minor response in three, and stable disease in ten [42]. A phase II trial of [^{90}Y-DOTA^0, Tyr^3]octreotide treatment in patients with small cell lung cancer and breast cancer started recently (Novartis B103 trial).

Dosimetry and critical organs

The critical organs for PRRT with radiolabelled somatostatin analogues, such as [^{111}In-DTPA^0]octreotide and [^{90}Y-DOTA^0, Tyr^3]octreotide, are the kidneys and bone marrow. The corresponding maximal tolerated doses for external radiation of these tissues are 23 and 2 Gy, respectively. Small (radio)peptides in the blood plasma are filtered through the glomerular capillaries in the kidneys and subsequently reabsorbed by and retained in the proximal tubular cells; as a consequence, radioactivity accumulates in the kidneys. Hammond et al. showed that this renal uptake in patients can be reduced by the intravenous infusion of basic amino acids lysine and arginine before, during and after the injection of the radioligand [43]. We showed that the renal uptake of [^{111}In-DTPA^0]octreotide in rats could be reduced by the administration of positively charged amino acids; for example, reductions of about 50% were achieved by single intravenous administration of 400 mg/kg L- or D-lysine [44]. Therefore, during clinical PRRT with radiolabelled octreotide or analogues, an infusion containing the positively charged amino acids L-lysine and L-arginine is nowadays given during and after the infusion of the radiopharmaceutical, in order to reduce the renal cortical uptake. The reported kidney doses for [^{111}In-DTPA^0]octreotide and [^{90}Y-DOTA^0, Tyr^3]octreotide range from 170 to 340 and from 780 to 2,240 cGy per 3,700 MBq, respectively. The corresponding values for bone marrow are 7–23 and 11–26, respectively ([34, 39, 45, 46, 47, 48]).

Future directions

As mentioned above, metabolically stable somatostatin analogues that bind all five somatostatin receptor subtypes are currently under development, as are analogues that are somatostatin receptor subtype-selective (e.g. Yang et al. recently reported somatostatin receptor subtype-selective peptomimetics [49]). The latter will allow more selective therapy of tumours, including those that express somatostatin receptors which do not bind octreotide (sst1 and sst4). PRRT with radiolabelled peptomimetics with appropriate particle ranges, including α-emitters [50], may become a new treatment modality.

The use of radiolabelled somatostatin analogues might also be considered firstly in an adjuvant setting to eradicate occult metastases after surgery of somatostatin receptor-positive tumours, and secondly for cancer recurrence at a later stage. In addition, Schally et al. reported successful antitumour effects of AN-238, an RC-160-like somatostatin analogue with high affinity for sst2, covalently bound to the cytotoxic 2-pyrrolino-doxorubicin [51]. This approach might open possibilities for multi-modality therapy of tumours expressing somatostatin receptors.

Transfection of somatostatin receptors

New developments in molecular biology have made it possible to transfect somatostatin receptor-negative tu-

mour cells with a somatostatin receptor gene. Several groups have developed an approach using *sst2* gene transfer for the treatment of cancer [52, 53]. By inducing the somatostatin receptor on pancreatic tumour cells, antitumour and bystander effects were obtained which might be attributed to several mechanisms ([52], and references therein). First, an autocrine negative feedback loop in which the transfected pancreatic tumour cells again start to produce somatostatin, which binds in an autocrine manner to the induced somatostatin receptor, may provide an inhibitory effect on tumour cell growth. Second, binding of somatostatin to sst2 upregulates *p27*, a tumour suppressor gene, which leads to cell cycle arrest in the G0–G1 phase, and subsequently causes apoptosis. Another reason why transfection of tumour cells with a somatostatin receptor gene may be beneficial is that it enables treatment with PRRT. Inducing the somatostatin receptor on somatostatin receptor-negative tumours makes possible treatment with radionuclides and other modalities targeted via this receptor (see above). Moreover, transfection of somatostatin receptor-positive tumours with a somatostatin receptor gene can increase the homogeneity and density of distribution of tumour cells which already express the somatostatin receptor, and so increase the efficacy of PRRT.

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